## REMARKS

Summary of the Office Action

With the previous cancellation of claims 1, 5-12, and 21, claims 2-4, 13-20, and 22-31 are pending in this application. Claims 2-4 and 13-20 are withdrawn from consideration due to a restriction election. Claims 22-31 are therefore currently under examination. Claims 27 and 28 were objected to because of informalities. Claim 31 stands rejected under 35 U.S.C. § 112, second paragraph. Claims 22-31 stand rejected under 35 U.S.C. § 112, first paragraph. Each of these rejections is addressed as follows.

Amendments

Claims 4 and 15 have been amended to correct typographical errors. New claim 32 has also been added. Support for this claim is found throughout the specification, for example, at paragraph 14 when read in combination with Example 3, paragraphs 81-87. No new matter has been added.

Informalities

Claims 27 and 28 were objected to on the grounds that the term "where" as recited in claim 27 should be changed to – wherein – , and the alternative operator "or" is repeated twice in claim 28 and should only be used once. The present amendment addresses both of these issues, and the objection to claims 27 and 28 should therefore be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 31 was rejected under 35 U.S.C. § 112, second paragraph as being indefinite. In particular, the Office has deemed the claim indefinite because the reference to figures 8 and 9 fails to illustrate the recited sequences. To address this issue, claim 31 has been amended to refer to figures 12 and 13. This rejection may now be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (new matter)

Claim 31 was rejected under 35 U.S.C. § 112, first paragraph as containing new matter. In particular, the Office has indicated that there is no support for the phrase "80% identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9." For the following reasons, this rejection may be withdrawn.

As an initial matter, as discussed above, claim 31 has been amended to reference figures 12 and 13.

The Office has indicated that the passage of the specification in paragraph 48 of the application "refers to ligands rather than antibodies." Applicants however direct the Office's attention to the general meaning of the term "ligand" as recited in paragraph 28 of the application as filed which includes an antibody as a ligand. Moreover, the Office is directed to the first sentence of paragraph 48, where it is stated:

> The invention further provides a pharmaceutical composition for the prevention or treatment of systemic inflammatory response syndrome and/or sepsis and/or septic shock and/or thrombus formation in the microvasculature and/or disseminated intravascular coagulation in mammals, comprising as an active ingredient a *ligand*, preferably other than a polyclonal antibody, *more preferably a human monoclonal antibody* such as disclosed hereinabove, in admixture with one or more pharmaceutically acceptable carriers (emphasis added).

From this passage it is clear that the term ligand is used in the present application to include an antibody. Additional examples of such usage are found, for example, (emphasis added) at: paragraph 31, lines 1-3 ('The term "homology" or "homologous" as used herein with reference to *ligands* in accordance with the present invention (*such as antibodies*) refers..."); paragraph 37, lines 2-3 ("...by selecting certain *ligands*, *such as human or humanized monoclonal antibodies or fragments or homologues thereof*...'); and paragraph 38, lines 12-14: ('The present invention also includes *ligands* other than polyclonal antibodies, *in particular monoclonal antibodies* which reduce the release rate of factor VIII...').

Finally, without acquiescence to the Office's objection, claim 31 has been amended

to refer to at least 80% sequence identity within the CDR regions identified in figures 12 and 13. Support for this amendment is found throughout the specification, for example, at paragraph 48, lines 14-18 ("The degree of homology with the said monoclonal antibody is preferably at least 80% ..., and the homology is preferably particularly in respect to the complementarity determining regions of the antibody."). In view of these comments and amendment, the rejection of claim 31 under 35 U.S.C. § 112, first paragraph (new matter) should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (deposit)

Applicants include a Declaration by co-inventor, Dr. Marc G. Jacquemin, stating that the deposit, LMBP 5089CB, shall be maintained for a term of at least thirty (30) years or five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the BCCM™ or for the enforceable life of the patent for which the deposit was made, as well as indicating that any restrictions on the availability to the public of cell line LMBP 5089CB will be irrevocably removed upon the granting of a patent on this application, with the exception of those restrictions listed in 37 C.F.R. § 1.808(b). This rejection should therefore be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

Claims 22-31 were rejected, under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Office, in general, asserts that the specification does not enable (i) production of a monoclonal antibody against factor VIII or an antigen-binding fragment of the monoclonal antibody and (ii) a method for preventing and/or treating Systemic Inflammatory Response Syndrome ("SIRS") using such antibodies or antigen-binding fragments. Applicants respectfully disagree.

The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent enable a person skilled in the art to make and use the claimed invention. "Patents ... are written to enable those skilled in the art to practice the invention." *Lindemann Machinenfabrik GMBH v. American Hoist & Derrick Co.,* 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1985). A patent specification need not explicitly teach those in the art

to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988); *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 954 (1987) ("A patent need not teach, and preferably omits, what is well known in the art.") The Patent Office bears the burden of clearly and convincingly proving facts showing that the claims are not enabled. *E.g.*, *In re Marzocchi*, 439 F.2d 220 (CCPA 1971) ("[A] specification disclosure which contains a teaching in the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (emphasis original).")

Applicants' written specification fully enables the practice of their claimed invention because the monoclonal antibodies or antigen-binding fragments thereof needed to practice the claimed methods are readily made using materials and routine methods that were known in the art and described in their specification. In view of these teachings and the state of the art, the Office contends that the claims are unpatentable for lack of enablement. In particular, the Office posits that the specification does not enable an ordinarily skilled artisan to practice the full scope of the claims because "undue experimentation would be required to produce the antibodies of the invention commensurate with the scope of the claims from the written disclosure alone." In support, the Office points to evidence – Rudikoff et al. (*Single amino acid substitution altering antigen-binding specificity*, Proc. Natl. Acad. Sci. 79: 1979-1983, 1982) – which it believes shows that one of ordinary skill could produce other antibodies falling within the scope of Applicants' claims only after undue experimentation, and therefore contends that this

evidence supports nonenablement.

Applicants note that "enablement is not precluded by the necessity for some experimentation such as routine screening." *Wands*, 858 F.2d 731, 740. Applicants' written specification provides considerable direction and guidance on how to practice their invention and presents several working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed for the production of the antibodies or antigen-binding fragments used in the claimed methods were well known. Nonetheless, to challenge the teachings of Applicants' specification, the Office relies on Rudikoff for allegedly teaching that "a single alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in loss of antigen-binding function." From this teaching, the Office concludes that it is "unlikely that the antibody defined by the claims ... would have the required binding function."

As an initial matter, Applicants note that Rudikoff, contrary to the Office's assertion, does not stand for such a broad proposition. Rudikoff explicitly, at page 1982 (col. 1), states: "It is clear that all such substitutions [single amino acid substitutions] need not and probably do not affect antigen binding." In view of this statement alone, the Office's reliance on Rudikoff is misplaced. Moreover, dependence on Rudikoff is inappropriate, in this case, given that "practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Wands*, 858 F.2d 731, 740. Applicants' specification clearly teaches one skilled in the art methods to screen for antibodies and antigen-binding fragments that recognize the C1 domain of factor VIII. Such screening is routine and cannot constitute undue experimentation. In addition, given that Applicants' specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a particular embodiment of the claimed invention, there is again no undue experimentation.

Moreover, with respect to claim 31, any "experimentation" involved in isolating and characterizing sequences having 80% sequence identity to Applicants' disclosed complementarity determining regions (CDRs) is straightforward and routine, and is rendered so by Applicants' discovery of these CDRs encoding the immunoglobulin

variable regions of the monoclonal antibody produced by the cell line named KRIX-1. Specifically, if one skilled in the art produced additional variable region sequences, they would simply use, for example, Applicants' disclosed CDR sequences as a template in combination with conventional mutagenesis methodologies used at the time the application was filed, such as alanine scanning, site-directed mutagenesis, or codon-based mutagenesis.[1] Monoclonal antibodies having sequences encoding variable regions that include, for example, at least part of an immunoglobulin variable region falling within the scope of the claims are then tested for binding to the C1 domain of factor VIII and the ability to partially inhibit factor VIII, for example, using the assays outlined in Applicants' specification. (See, for example, Examples 3 and 5.) Accordingly, there is no basis for concluding that one skilled in the art, once equipped with Applicants' disclosed CDR sequences within the heavy and light chain variable regions, would not be able to obtain a reasonable number of antibodies, binding to the C1 domain of factor VIII comprising variable heavy chain sequences comprising CDR regions with at least 80% sequence identity to the amino acid sequence of the CDRs depicted in figure 12 and/or variable light chain sequences comprising CDR regions with at least 80% sequence identity to the amino acid sequence of the CDRs depicted in figure 13, as presently claimed.

Applicants also point out that, to sustain an enablement rejection, the Office has the initial burden to establish a reasonable basis to question the enabling nature of an Applicants' specification. Thus, in a case in which the PTO questions the enablement of a claim, the CCPA, in *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) has stated that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling

[1] See, for example, Near et al., Characterization of an Anti-Digoxin Antibody Binding Site by Site-Directed Mutagenesis, *Molecular Immunology* 30:369-377, 1993 (copy enclosed); Chatellier et al., Codon-Based Combinatorial Alanine Scanning Site-Directed Mutagenesis: Design, Implementation, and Polymerase Chain Reaction Screening, *Analytical Biochemistry* 229:282-290, 1995 (copy enclosed); and Yelton et al., Affinity Maturation of the BR96 Anti-Carcinoma Antibody By Codon-Based Mutagenesis, *The Journal of Immunology* 155:1994-2004, 1995 (copy enclosed).

> requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (emphasis added).

The MPEP (§ 2164.04) further emphasizes the *Marzocchi* standard in stating that:

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure (emphasis added).

Here, Applicants note that no scientific evidence currently made of record in this case establishes a basis for doubting the objective truth of the statements found in Applicants' specification regarding enablement with respect to isolating CDRs falling within Applicants' claims and determining whether such sequences bind to and partially inactivate factor VIII. On this basis, as well, the facts in the present case compel withdrawal of the § 112, first paragraph enablement rejection, and Applicants request reconsideration on this issue.

In short, the Office provides no substantial evidence that conclusively shows that one of ordinary skill following the techniques disclosed in the specification could produce other antibodies requiring the claimed characteristics only after undue experimentation. Because it is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation, the Office's evidence concerning Applicants' specification, with respect to identifying antibodies or antigen-binding fragments thereof that bind to the C1 domain of factor VIII, is insufficient as a matter of law.

The Office has also indicated that there is insufficient enablement for the claims relating to methods for preventing and/or treating SIRS in a mammal using the monoclonal antibodies or antigen-binding fragments thereof of the invention. In particular, the Office argues that Applicants' disclosure "does not appear to have provided the skilled artisan with sufficient guidance and support as how to reach the development of effective *in vivo*

human therapeutic methods, commensurate in scope with the claimed invention." Applicants disagree.

Lack of enablement of Applicants' invention cannot be predicated on the Office's reliance on Freeman et al. ("The role of inflammation in sepsis and septic shock: in inflammation: Basic principles and clinical correlates," 3rd ed., edited by John I. Gallin and Ralph Synderman, published by Lippincott Williams & Wilkins, Philadelphia, pages 965-975, 1999) and Taylor et al. ("E3 F(ab')2, a monoclonal antibody to the platelet GPIIb/IIIa receptor, ... and sublethal infusion of Escherichia coli." Blood 89:4078-4084, 1997). This evidence provided by the Office does not meet the requisite standard of proof. Freeman deals only with anti-inflammatory agents and does not even mention prevention of coagulation for treating septic shock much less SIRS. Freeman is irrelevant to Applicants' claimed invention.

Taylor is cited by the Office for the proposition that the "differences in pathophysiology between this model [baboon] and each of the human disorders makes it very difficult to extrapolate from this model [baboon] to human disease." Applicants first note that Taylor's methodology, unlike Applicants, inhibits Protein C. As noted in Applicants' previous response, it is precisely this inhibition which is prevented in the present invention, as partial inhibition of factor VIII makes it possible to preserve Protein C activity. In addition, on this point, the Office's attention is directed to the specification, for example, at paragraph 14 where a particular object of the invention is a method for "restoring the plasma level of . . . activated protein C." On this basis alone, Taylor is an apples and oranges comparison and, like Freeman, is essentially irrelevant to the claimed method of treatment.

Even assuming *arguendo* that Taylor is deemed relevant, Applicants note that Taylor gives no warning of extrapolating animal results to humans in general. Nothing in the Taylor article would cause one of skill in the art to reasonably doubt the asserted usefulness of Applicants' claimed method. Indeed, Taylor does not question the usefulness of any of Applicants' claimed compounds in treating SIRS or provide any evidence to cause one skilled in the art to question the asserted utility of the claimed methods. Finally, the purpose of treating SIRS using an antibody or antigen-binding

fragment thereof does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. See, for example, *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436,1441 (Fed. Cir. 1995) ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicant to provide rebuttal evidence sufficient to convince such a person of the inventions asserted utility." (emphasis added).)

Applicants further assert that if the enablement requirement for treatment methods in humans were erroneously interpreted to require a "perfect" animal model for treating SIRS then the scope of patentable subject matter would be greatly diminished because there are few, if any, human diseases for which a perfect non-human animal model exists. Indeed, at the time of Applicants' invention, since there were reliable experimental animal models for testing the effects of compounds in treating sepsis (see, for example, Yan et al, *Nature Medicine* 10:161-167, 2004 (copy enclosed) which describes three mouse models of sepsis and Martinell et al., *Eur Surg. Res.* 17:160-6, 1985 (copy of abstract enclosed) , it would be an undue burden on Applicants to require a "perfect" animal model. Moreover, Applicants note that numerous therapeutic methods have been patented and clinically approved without the existence of such a "perfect" model. In short, given that reliable animal models for human SIRS exist, the absence of a "perfect" model cannot form the basis for the enablement rejection in this case.

Applicants also note that the Office's reliance on *Ex parte Krepelka*, 231 USPQ 746 and *Ex parte Mass*, 9 USPQ2d 1746 is misplaced. While both opinions refer to requiring "substantiating evidence," such evidence was required where the "utility in question is sufficiently unusual to justify an Examiner's requiring substantiating evidence." No evidence or reasoning has been provided indicating that Applicants' claimed method of treatment is unbelievable. Indeed, others have used an antibody for treating sepsis and septic shock. See, for example, Begany ("Monoclonal antibody improves sepsis." Pulmonary Reviews.com (http://www.pulmonaryreviews.com/aug00/pr_aug00_TNF.html); copy enclosed) which described the use of afelimorab in treating sepsis or septic shock. In addition, Applicants direct the Office's attention to Ziegler et al. (*New England J. Med.* 324:429-436, 1991) which describes a human monoclonal IgM antibody that binds

specifically to the lipid A domain of endotoxin and prevents death in laboratory animals with gram-negative bacteremia and endotoxemia. Ziegler subsequently concluded that the monoclonal antibody is safe and effective for the treatment of human patients with sepsis and gram-negative bacteremia. The Office's doubt therefore is unreasonable in light of the utility alleged by Applicants.

Finally, on the issue of the general efficacy of Applicants' claimed methods, the Office is directed to the accompanying Declaration under 37 C.F.R. § 1.132 of Dr. Jean-Marie Saint-Remy dated October 13, 2005, which describes the effectiveness of antibodies, KRIX-1 and a deglycosylated form thereof designated Krix-1Q,[2] against sepsis in a mouse model system. Moreover, Applicants, as is discussed above, note that the mouse model used in this study is well-established and customarily used for the screening of agents of potential utility in the treatment of humans (see also, paragraph 5 of Dr. Saint-Remy's Declaration). Further, Applicants note that "[s]epsis represents a SIRS associated to infection" (see, for example, Applicants' specification at ¶ 3). Such evidence strongly supports the patentability of the claimed methods.

In further view of these *in vivo* data, Applicants' note that they have also provided *in vitro* data demonstrating the partial inhibition of thrombin formation with a first anti-factor VIII C1 domain antibody partially inhibiting factor VIII activity (Example 5). Here, administration of the partially inhibiting antibody to whole blood samples *in vitro* resulted in a reduction (but not abolishment) in the rate of thrombin formation. Furthermore, Applicants direct the Office's attention again to Declaration of Dr. Jean-Marie Saint-Remy. In paragraphs 10-17 of this Declaration, Dr. Saint-Remy describes results for still another antibody, designated RHD5, which binds the C1 domain of factor VIII and also partially inhibits factor VIII activity. Because thrombin plays an essential role in disseminated intravascular coagulation ("DIC") associated with SIRS, including sepsis, reduction of thrombin formation, regulated in part by factor VIII, will therefore reduce DIC and SIRS including sepsis. Applicants' *in vitro* testing of a partial inhibitor of factor VIII therefore

[2] Applicants note that Krix-1Q was previously referred to as 2E9Q and LE2E9Q in the Saint-Remy Declaration dated November 11, 2004.

substantiates the belief that such a partial inhibitor of factor VIII will also be successful in treating or preventing SIRS. See *Cross v. Iizuka,* 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)("a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based on probative evidence.") Absent a reason why one skilled in the art would not accept Applicants' *in vitro* results as reasonably correlating to the condition being treated, this ground of rejection should be withdrawn. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)(reversing the PTO decision based on finding that in vitro data did not support *in vivo* applications).

In view of the above evidence, Applicants respectfully assert that one skilled in the art would appreciate that the presently claimed methods can be used to prevent and/or treat SIRS in a mammal. It has been established that the specification need not explicitly teach every possible embodiment of the invention. Furthermore, the success of all possible therapies of the invention in humans is not necessary for enablement of the claims. The case law is clear that enablement does not require absolute predictability for carrying out all possible embodiments of a claimed method. Rather, the law merely requires that the specification, in combination with the art, provide a description that allows a reasonable number of species falling within the claim to be made and used without undue experimentation. *In re Wands* (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Since the Patent Office, in this case, has not offered any evidence that proves that instantly claimed invention would require undue experimentation to practice, it has not carried its burden of showing a reasonable basis to doubt the enablement of the present claims.

Applicants' specification provides sufficient guidance so that no undue experimentation is required to administer to a mammal an antibody or antigen-binding fragment thereof that recognizes epitopes in the C1 domain of factor VIII for the prevention and/or treatment of SIRS. Applicants outline, in the specification, therapies that can be administered using standard methods for the treatment of SIRS. Moreover, Applicants have demonstrated that the methods presently claimed are effective in partially inhibiting thrombin formation *in vitro* and, as described, in the accompanying Declaration of Dr. Saint-Remy in an *in vivo* mouse model of preventing sepsis, further evidencing the general

applicability of these methods. In light of Applicants' teachings and the evidence presented herein demonstrating the workability of the claimed methods, the enablement rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph (written description)

Claims 22-31 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. For the following reasons, this rejection should be withdrawn.

The written description requirement serves "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material." *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (C.C.P.A. 1976). In order to meet the written description requirement, Applicants need not utilize any particular form of disclosure to describe the subject matter claimed, but "the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citation omitted). Stated another way, "the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

In this case, the specification teaches one of ordinary skill a method for preventing and/or treating a systemic inflammatory response syndrome (SIRS) in mammals. The Summary of the Invention, Detailed Description of the Invention, and Example portions of the specification discuss thoroughly the claimed methods. For example, evidence from the specification itself supporting the written description of claim 22 is as follows:

| Claim limitation | Support in '569 application |
|---|---|
| | |
| A method for preventing and/or treating Systemic Inflammatory Response Syndrome in a mammal by administering a partial inhibitor of factor VIII to the said mammal | ¶ 14: The present invention first provides a method for preventing and/or treating a systemic inflammatory response syndrome (SIRS) in mammals ... by administering a partial inhibitor of factor VIII to the mammal in need thereof. |
| | |
| which is a monoclonal antibody against factor VIII or an antigen binding fragment of said monoclonal antibody, | ¶ 37: The present invention relates to a general concept of only partially inactivating factor VIII by selecting certain ligands, such as human or humanized monoclonal antibodies or fragments or homologues thereof, and using them in methods and therapeutic compositions for preventing and/or treating systemic inflammatory response syndrome (SIRS) |
| | |
| said antibody or fragment being able to recognize epitopes located in the C1 domain of factor VIII. | ¶ 38: [M]onoclonal antibodies and fragments may target a domain of factor VIII, in particular the C1 domain of factor VIII. |

The specification unambiguously informs skilled artisans to administer a partial inhibitor of factor VIII to a mammal which is a monoclonal antibody against factor VIII or an antigen-binding fragment of the monoclonal antibody. Furthermore, the specification unambiguously informs the skilled artisan that the antibody or fragment recognizes epitopes located in the C1 domain of factor VIII. The claim terms at issue here are not new or unknown compounds or include structures that ordinarily skilled artisans would easily miscomprehend. Indeed, phrases such as "partial inhibitor," "monoclonal antibody against factor VIII," "an antigen binding fragment of said monoclonal antibody," or "antibody or fragment being able to recognize epitopes located in the C1 domain of factor VIII," readily "convey[] distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1567-1568, 43 USPQ2d at 1406 (Fed. 1997). Indeed, the specification's description of producing the antibodies used in the

claimed method (see, for example, Example 1, Example 2, and Example 4) adequately supports claims covering methods of using a monoclonal antibody against factor VIII or an antigen-binding fragment of the monoclonal antibody (as a partial inhibitor of factor VIII ) that recognize epitopes located in the C1 domain of factor VIII, rendering the Office's argument that Applicants' "specification provides neither a representative number of species or antibody ... to describe the claimed genus, nor does it provide a description of structural features that are common to species" unavailing. Moreover, the Office supplies no substantial evidence showing that skilled artisans would be unable to understand the specification's teachings. In sum, Applicants' specification shows that the inventors possessed the claimed invention at the time of filing and the written description rejection, on this basis alone, should be withdrawn.

In connection with claim 31 and the Office's assertion that the specification neither describes the claimed species nor describe structural features that are common to species, Applicants respectfully assert that further characterization of the compositions used in the claimed method is not necessary to distinguish the compositions that fall within the scope of the claims. As stated in the Written Description Guidelines (66 FR 1106),

> [f]actors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The compositions used in the claimed methods are distinguished from other compositions by both (i) the structural characteristic of having CDR regions in its variable heavy chain sequence with at least 80% sequence identity to the amino acid sequence of the CDRs depicted in figure 12 and/or including CDR regions in its variable light chain sequence with at least 80% sequence identity to the amino acid sequence of the CDRs depicted in figure 13 and (2) the specific functional characteristic of recognizing the C1

domain of factor VIII. Based on Applicants' disclosure of these properties and routine assays for determining whether a particular composition has these properties, one skilled in the art would appreciate that Applicants were in possession of the compositions for use in the claimed methods.

As clear distinguishing characteristics that are shared by the compositions used in the claimed methods are disclosed in Applicants' specification, the written description rejection should be withdrawn.

## Conclusion

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested. If the Office does not concur, an interview with the undersigned is hereby requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 18 October 2005

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